BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Image

1636

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of
CHARO et al.
Appln. No. 09/763,462
Filed: May 1, 2001
FOR: METHOD OF DNA VACCINATION

Confirmation No.: 7394
Atty. Ref.: 1430-264
Group Art Unit: 1636
Examiner: C.X. Qian

* * *

SUPPLEMENTAL RESPONSE

February 2, 2004

U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the response filed November 25, 2003, attached for the Examiner's consideration is the Declaration of John R. Rhodes. Reconsideration is requested.

Applicants submit that this application is in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,
NIXON & VANDERHYE P.C.

By: _____
Gary R. Tanigawa
Reg. No. 43,180

1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

CHARO et al.

Appln. No. 09/763,462

Filed: May 1, 2001

FOR: METHOD OF DNA VACCINATION

Confirmation No.: 7394

Atty. Ref.: 1430-264

Group Art Unit: 1636

Examiner: C.X. Qian

DECLARATION OF JOHN R. RHODES

I, John R. Rhodes, declare the following:

1. I earned a Ph.D. degree in immunology from The University of London.

2. I am the Director of Disease Strategy (Immunotherapeutics) at Glaxo Smith Kline Medicines Research Centre and a Fellow of the Royal College of Pathologists.

3. I have more than 20 years of post-graduate research experience in the field of immunology. In particular, I have conducted and supervised research using immuno-adjuvants. Attached is a copy of my curriculum vitae which describes this work.

4. I am the inventor of U.S. Patent 5,508,310, which discloses the use of a novel class of immunoadjuvants. These compounds are also used in this patent application to enhance the immune response initiated by a DNA vaccine. They include tucaresol or 4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid.

5. I am familiar with the invention claimed in this patent application and the prior art rejections made against those claims.

6. On information and belief, I understand that the claims being examined were rejected as allegedly obvious over the prior art. The primary references relied upon in the Examiner's rejections are Rhodes (U.S. Patent 5,508,310) and Herrmann et al. (U.S. Patent 5,620,896).

7. On information and belief, I understand that it was alleged in the Office Action mailed March 11, 2003 that the claims are obvious because (a) one of ordinary skill in the art would have been motivated to make the combination/modification of the prior art proposed by the Examiner because it was believed that both DNA and protein vaccines initiate immune responses by the same mechanism and (b) there

was a reasonable expectation, according to the Examiner, that the compounds recited in the claims (e.g., tucaresol) would enhance the immune response initiated by a DNA vaccine because they were known adjuvants for a protein vaccine. I respectfully disagree with these allegations for the reasons detailed below.

8. My patent's specification defined an **immunopotentiator** as "an agent which is capable of restoring a depressed immune function, or enhancing normal immune function, or both" (column 1, lines 52-57). Subsequently, **immune function** was defined as "the development and expression of humoral (antibody-mediated) immunity, cellular (T-cell-mediated) immunity, or macrophage and granulocyte mediated resistance" (column 5, lines 24-28). Schiff base forming compounds (e.g., tucaresol) could be used as adjuvants for protein vaccination (see column 14, lines 33-37). But use of such compounds was restricted to protein vaccines and protein vaccination. There was neither teaching nor suggestion in my patent's specification that Schiff base forming compounds could be successfully used in the context of enhancing the immune response to a DNA vaccine or DNA vaccination with a nucleotide sequence encoding an antigenic peptide. The Herrmann et al. patent also did not contemplate the use of Schiff base forming compounds to enhance the immune response to a DNA vaccine or DNA vaccination.

9. Tucaresol exerts its effects by amplifying co-stimulatory or 2nd signals of the immune response. The mechanism of handling protein antigens produced during an infection or contained in conventional vaccines (see ref. 1 of Appendix I) differs from the way DNA-encoded antigens are handled in a number of fundamental ways. In an infection, antigens are generated by: pathway A in which the synthetic machinery of the host cell is taken over by the virus for the production of viral proteins (see Fig. A of Appendix II) or pathway B in which whole microbes or fragments of microbes are taken up from the intercellular environment by phagocytic cells and then degraded (see Fig. B of Appendix II).

10. The same two pathways operate for conventional vaccines in which pathway A predominates for live attenuated vaccines and pathway B predominates for killed and subunit vaccines. Importantly, both pathways provide an array of danger signals and co-stimulatory signals initiated by pathogen associated molecular patterns (PAMPs) during the uptake/entry phase into antigen presenting cells (refs. 2-4 of Appendix I).

11. In contrast, antigens encoded by DNA vaccines are taken up in a different way and utilize a unique mechanism of antigen handling that involves neither of these pathways. Importantly, DNA vaccines do not contribute to amplification of the danger/co-stimulatory signals initiated by PAMPs and other microbial elements. This is illustrated in Fig. C of Appendix II which shows that DNA directly transfects the cell and lacks the microbial elements that amplify co-stimulation (ref. 5 of Appendix I).

12. Subsequent events in terms of binding to MHC molecules and ligating the T-cell receptor are the same for all three kinds of delivery (ref. 1 of Appendix I). The important difference is in the co-stimulatory environment which is absent in DNA vaccination as shown in pathway C (see Fig. C of Appendix II). Adjuvants exert their effects on the co-stimulatory environment (ref. 6 of Appendix I) and both conventional adjuvants and tucaresol are effective in pathways A and B. It was therefore surprising that tucaresol was found to work in the case of DNA vaccination (i.e., pathway C) where the co-stimulatory environment is absent or very weak.

13. Adjuvants work through co-stimulatory mechanisms and do not affect the recognition of antigen by the T-cell receptor or the signal it transduces (refs. 6-7 of Appendix I and see Fig. D of Appendix II). Instead, they work through ancillary receptors such as toll-like receptors to amplify co-stimulation (ref. 8 of Appendix I). Accessory/co-stimulatory signals are known to be interdependent and integrated at a number of levels within antigen presenting cells and T cells (ref. 9 of Appendix I). Tucaresol also exerts its effects on co-stimulation (ref. 10 of Appendix I). Because the co-stimulatory environment associated with conventional protein vaccines (and natural infections) is very different from the co-stimulatory environment associated with DNA vaccination, there would not be a reasonable expectation of success in using tucaresol with DNA vaccines and DNA vaccination.

14. During 1995-1996, large animal studies were indicating that adjuvants were likely to be needed for DNA vaccination and there was an expectation that, because of the fundamental differences between DNA vaccination and other forms of vaccination (e.g., using protein vaccines), adjuvants that worked for conventional protein vaccines would be unlikely to work for DNA vaccines (ref. 8 of Appendix I). It is for this reason that other approaches such as co-administering cytokines were pursued rather than adjuvants previously used for protein vaccines such as tucaresol (ref. 9 of Appendix I).

15. Known immunopotentiating agents have been tried in combination with DNA vaccines (as disclosed on page 3, lines 27-35, of this specification) with limited or mixed success and the conventional adjuvants such as alum, FCA, and FIA are not effective as adjuvants in DNA vaccination, as demonstrated in Example 1 of this specification. A person of skill in the art would thus not have had a reasonable expectation that adjuvants successfully used in conventional protein vaccination would also be effective as adjuvants in DNA vaccination. It was all the more surprising therefore that Schiff base forming compounds such as tucaresol, an effective conventional vaccine adjuvant, could be successfully used in a DNA vaccine setting. The Examiner is therefore incorrect in citing my patent as teaching the usefulness of tucaresol in a DNA vaccine setting or even that there would be any motivation to use tucerasol in such a setting with any expectation of success.

16. The other patent cited by the Examiner, Herrmann et al., does not disclose any particular adjuvants or classes of adjuvants which might be expected to work, and provides no working examples using any such adjuvant. Moreover, the purpose of the adjuvant described by the Herrmann et al. patent is to "promote DNA uptake" or "recruitment of immune system cells to the site." Such compounds might be termed adjuvants in the Herrmann et al. patent, but they are not the same as agents which would "enhance both humoral and cellular immune responses initiated by the antigenic peptide" as required by the pending claims. This establishes that the term "adjuvant" is used to serve completely different purposes in the two patents. The Herrmann et al. patent would not therefore provide any additional motivation to that disclosed in my patent, and in view of the lack of success reported with conventional adjuvants in enhancing the immune system's response to DNA vaccines, no expectation of success can be derived from the Herrmann et al. patent of "adjuvants" which are intended to serve a completely different function.

17. The combined teachings of my patent and the Herrmann et al. patent would not therefore suggest to a skilled artisan that Schiff base forming compounds such as tucaresol, will achieve enhancement of the immune response in a DNA vaccine setting, where other conventional adjuvants will not, nor that such compounds will achieve this utility by enhancing both the humoral and cellular immune responses initiated by the antigenic peptide expressed by the nucleotide sequence which forms the DNA vaccine.

18. Therefore, for the above reasons, I conclude that (a) one of ordinary skill would not have been motivated to make the combination/modification of prior art proposed in the Office Action and (b) there was not a reasonable expectation of success to use the compounds recited in the claims to enhance the immune response initiated by a DNA vaccine.

19. The undersigned declares that all statements made herein of my personal knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that any willful false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of this patent application or any patent issuing thereon.

Date: 2nd. Feb. 2004

John R. Rhodes

Appendix I

References

1. Klein, J. and Sato, A. Advances in immunology: The HLA system-First of two parts. New Eng. J. Med. 2000: 343; 702-709. Klein, J. and Sato, A.: 343; 782-786 Advances in immunology: The HLA system-second of two parts. New Eng. J. Med. 2000

2. Medzhitov R, Janeway CA. Innate immune response recognition and control of adaptive immune responses. Sem. Immunol. 1998; 10: 351-353.

3. Medzhitov R, Janeway CA. How does the immune system distinguish self from nonself? Sem. Immunol. 2000; 12:185-188.

4. Medzhitov R, Janeway CA. Decoding the patterns of self and nonself by the innate immune system. Science 2002; 296:298-300.

5. Donnelly JJ. Ulmer JB. Shiver JW. Liu MA. DNA vaccines. *Annual Review of Immunology. 15:617-648, 1997.*

6. Masihi KN. Immunomodulatory agents for the prophylaxis and therapy of infections. Int. J. Antimicrob. Agents 2000; 14:181-191

7. Delves, PJ and Roitt, IM. Advances in ImmunologyThe Immune system first of two parts. New Eng. J. Med. 2000: 343 37-49.

8. Seiling PA, Modlin RL. Toll-like receptors: mammalian 'taste receptors' for a smorgasbord of microbial invaders. Current Opinion in Microbiol. 2002; 5:70-75.

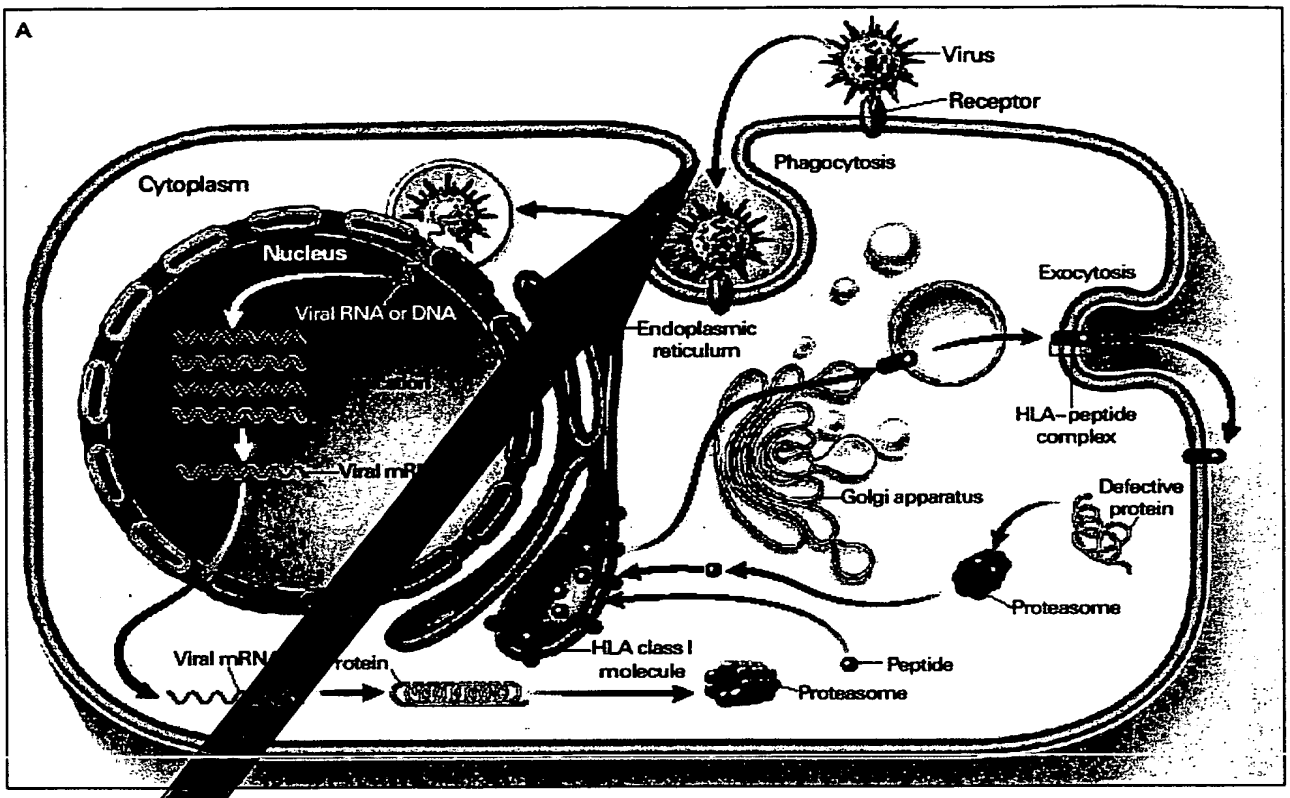
9. Bluestone JA, Khattri R, van Seventer GA. Accessory molecules. In Paul, W. ed. Fundamental Immunology 4th edn. Lippincot-Raven, New York 1999; 449-478.

10. Rhodes J, Chen H, Hall SR, Beesley JE, Jenkins DC, Collins P, Zheng B. Therapeutic potentiation of the immune system by costimulatory Schiff base-forming drugs. Nature 1995; 377:71-75.

11. Davis, HL, McCluskie, MJ, Gerin, JL, and Purcell, RH. DNA vaccine for hepatitis B: evidence for immunogenicity in chimpanzees and comparison with other vaccines. Proc. Natl. Acad. Sci. USA 1996; 93: 7213-7218 .

12. Boyer, JD, Cohen, AD, Ugen KE, Edgeworth, RL, Bennet, M, Shah, A, Schumann, K, Nath, B, Javadian, A, Bagarzzi, ML, Kim, J, and Weiner DB. Therapeutic immunisation of HIV-infected chaimpanzes using HIV-1 plasmid antignes and interleukin-12 expressing plasmids. AIDS 2000; 14: 1515-1522.

Appendix II



Figures A & B. Pathways A and B both contribute a diverse array of danger signals, pathogen associated molecular patterns and costimulatory signals during the entry/uptake phase. Conventional adjuvants (& tucaresol) are effective.

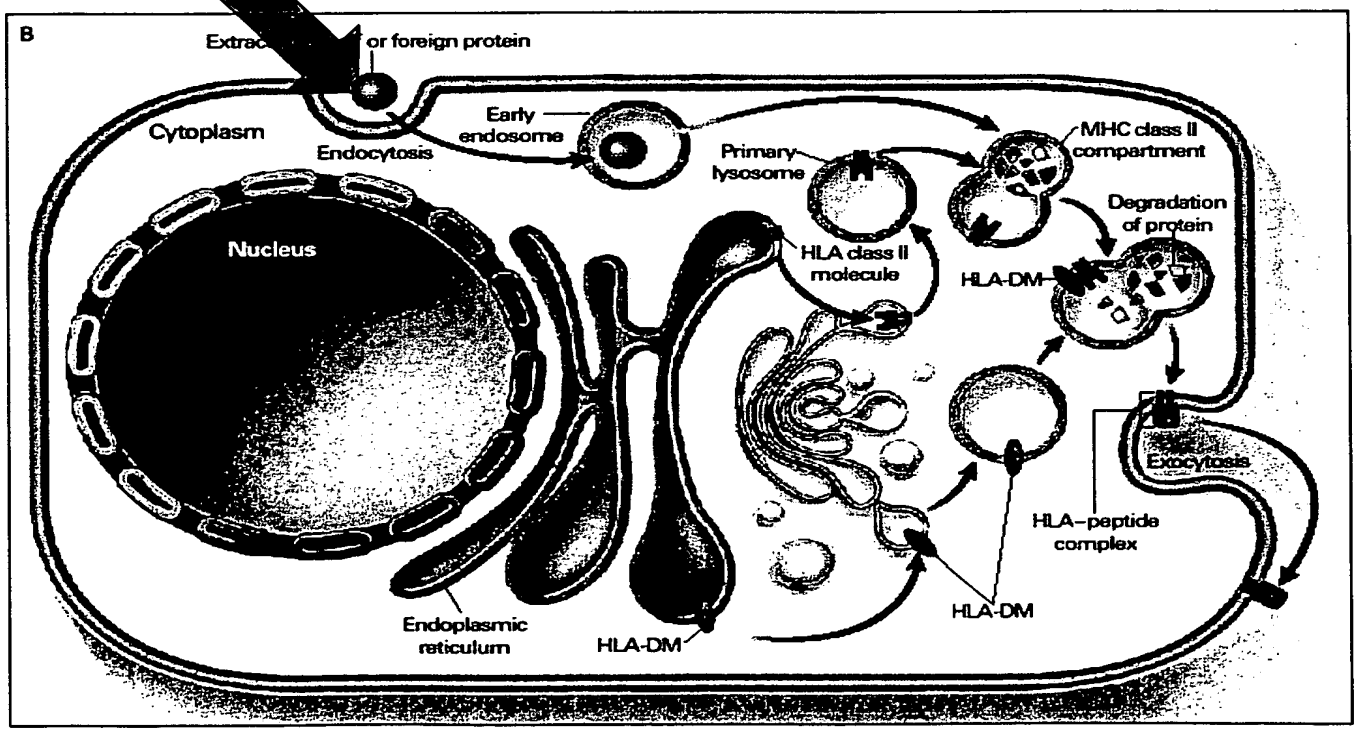


Figure C. Delivery of antigens as DNA provides no danger signals, no pathogen associated molecular patterns, and no modulation of the spectrum of costimulatory signals. Conventional adjuvants are ineffective. Tucaresol is effective.

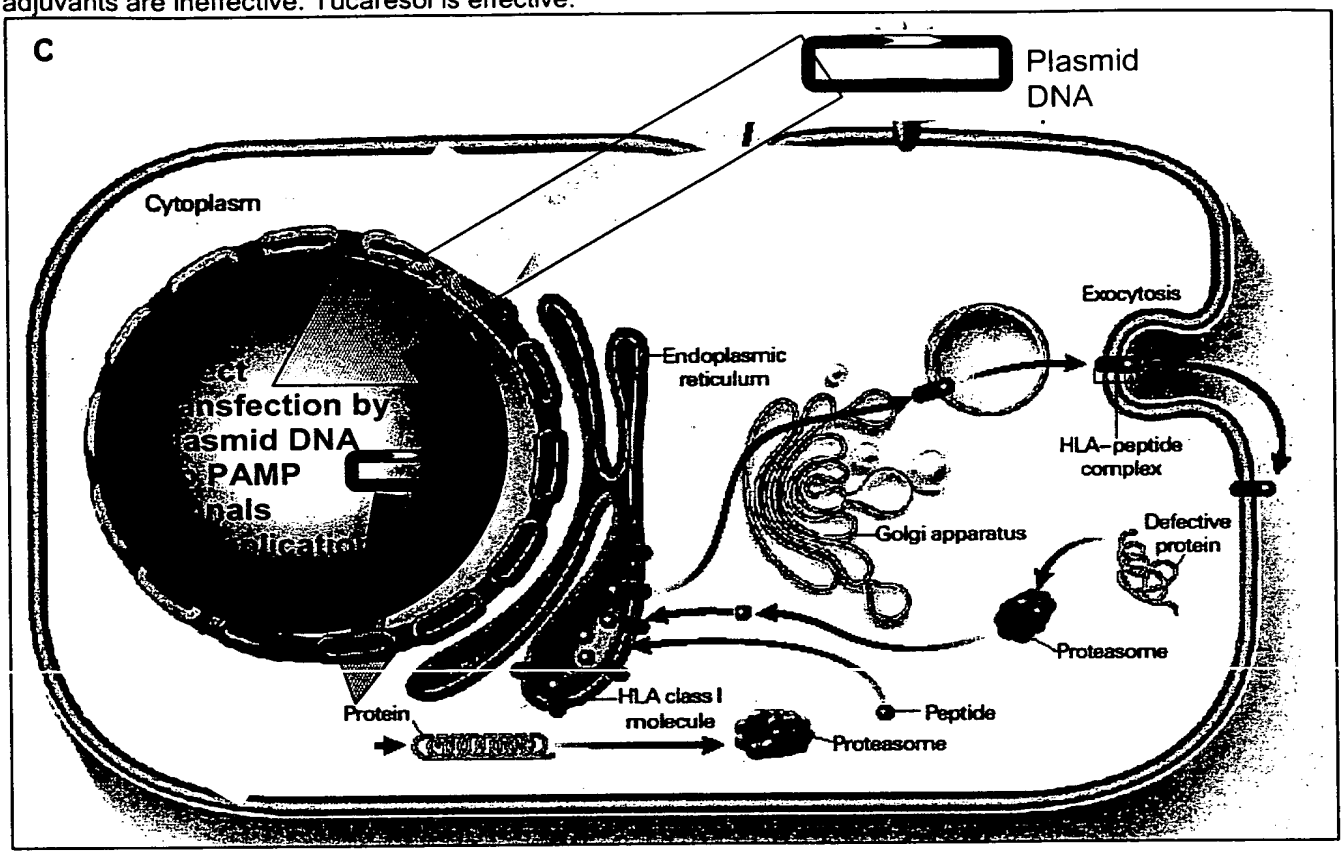
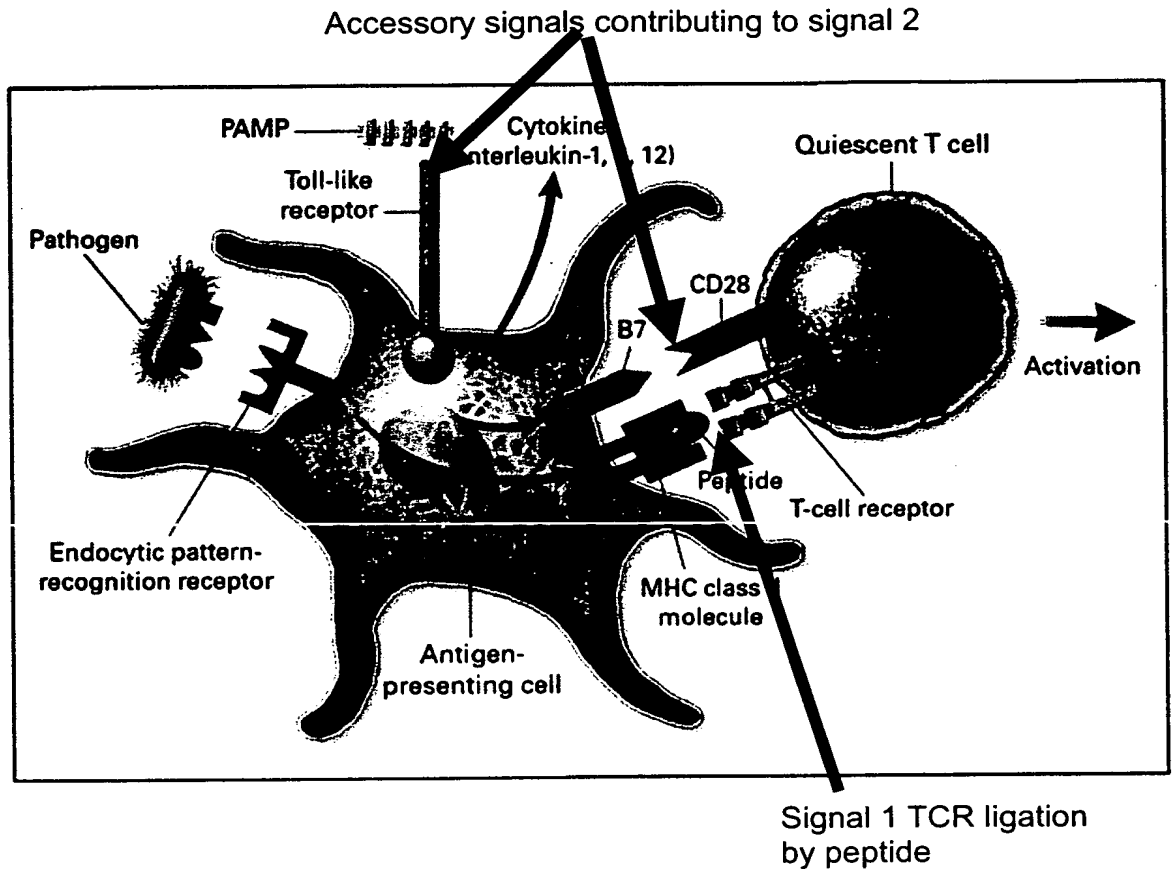


Figure D. Induction of immune responses requires two signals. Signal 1, ligation of the T-cell receptor by antigen is the same for natural infections, conventional vaccines and DNA vaccines. Signal 2 depends on events triggered by the entry/uptake of antigens in APC. Natural infections and conventional vaccination provide a number of danger/PAMP- associated signals (e.g. through toll-like receptors) during the entry uptake phase in APC. In contrast DNA vaccination does not provide these signals. Adjuvants work through the costimulatory pathways. Conventional and DNA vaccines are therefore fundamentally different with regard to adjuvant needs.



CURRICULUM VITAE

Name	JOHN RICHARD RHODES PhD FRCPath
Date of Birth	27th November 1947
Nationality	British
Marital Status	Married, 2 daughters
1966	Entered the Department of Zoology, University College, London (U.C.L.) after attending The Grammar School, Cambridge
1st year	Mathematics Organic chemistry Physical chemistry Statistics Cellular and molecular biology
2nd year	Biochemistry Mammalian physiology Neurophysiology General zoology Evolutionary zoology
3rd year	Animal cell biology Animal developmental biology Enzymology of subcellular component Physiology of the cerebral cortex Physiology of the spinal and peripheral nervous system Immunology
1969	B.Sc. (Upper second class honours) Registered for a PhD. degree in the University of London. Field of study: Immunology, Cellular Receptors (Supervisor - Dr. C.A. King, Additional mentors- Prof. M. Abercrombie, Prof. N.A. Mitchison)

Undergraduate office held:	**Chairman** Zoological Society, U.C.L.
1969-1972	**MRC Scholar** Department of Zoology, U.C.L.
1972-1973	**Margaret Browne Student** Department of Zoology, U.C.L.
1973 (March)	PhD. University of London Title of thesis : Investigation of receptors for immunoglobulins on guinea pig spleen and thymus cells and their significance in the immune response.
1973 (April) - 1974	**Visiting Fellow** National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, U.S.A. Mentors: Charles H. Kirkpatrick, Alan S. Rosenthal
1974-1977	**Beit Memorial Fellow** University of Cambridge. Holder - Cancer Research Campaign Project Grant in the Immunology Division (Head - Professor R.R.A. Coombs), Department of Pathology.
1977-1980	**Research Associate** University of Cambridge (Senior member, Wolfson College). Holder - Cancer Research Campaign Project Grant, Immunology Division, Department of Pathology.
1980-1982	**Senior Research Associate** Univ. of Cambridge. (Senior member, Wolfson College). Holder -Cancer Research Campaign Project Grant, Immunology Division, Department of Pathology.
July-August 1982	**Yamagiwa Yoshida Memorial International Cancer Study Award.** Department of Microbiology,

	University of Texas Medical Branch, Galveston, Texas 77550, U.S.A.
1982 - 1990	**Senior Scientist (Laboratory Staff)** Department of Experimental Immunobiology, Wellcome Research Laboratories and Wellcome Biotech, Beckenham, Kent, U.K.
1990-1993	**Group Leader, Immunopharmacology Group** Department of Pharmacology Wellcome Research Laboratories, Beckenham, Kent, BR3 3BS, U.K.
1993-1994	**Group Leader, Immunopharmacology Group** **Senior Research Scientist** (Executive Staff) Department of Pharmacology Wellcome Research Laboratories, Beckenham, Kent, BR3 3BS, U.K.
1994-95	**Senior Research Scientist** (Executive Staff) Executive member of the Molecular Immunology Group, Biology Division, Wellcome Research Laboratories, Wellcome Foundation plc
1995-Jan 2000	**Principal Scientist,** **International Project Leader** Immunology Unit Cellular Sciences Division, Glaxo Wellcome Medicines Research Centre, Stevenage, Hertfordshire
1998	Elected to Membership of the Royal College of Pathologists on the basis of published works. July 1998
2000-Jan 2001	**Acting Head, Molecular Immunology Unit** **International Project Leader** Molecular Immunology Unit Immunology and Virology Department Division of Biological Sciences

	Glaxo Wellcome Medicines Research Centre, Stevenage, Hertfordshire
Jan 2001-present	**Director, Disease Strategy** Immunotherapeutics, Discovery Research, Glaxo Smith Kline Medicines Research Centre, Stevenage, Hertfordshire
2003	Elected to Fellowship of the Royal College of Pathologists on the basis of published works.

Corporate role at Glaxo Wellcome R&D has included management of the Molecular Immunology Research Unit (28 staff), and leadership of the International Development Project on Glaxo Wellcome's first DNA vaccine – A therapeutic vaccine for chronic HBV infection. This project included preclinical and clinical activities, and was the subject of a number of regulatory submissions. The project carried responsibility for the PowderJect Particle Mediated Vaccine delivery technology platform with the associated Biopharmaceutical Development effort and coordination of collaborative activities with GW's alliance partner PowderJect.

Previous experience in drug discovery and development has included

- Fundamental research in Immunology leading to the characterisation of novel mechanisms in immune induction.
- The translation of fundamental observations into target identification strategies.
- The exploratory development of a novel class of immunopotentiatry drugs and adjuvants.
- Contributions to regulatory submissions, commercial analyses, and the design and execution of phase I/II Clinical Trials

PRINCIPAL PUBLICATIONS

1. **Rhodes, J.** Receptor for monomeric IgM on guinea-pig splenic macrophages. **Nature** 243:527-528 (1973).

2. **Rhodes, J.** Macrophage heterogeneity in receptor activity : The activation of macrophage Fc receptor function *in vivo* and *in vitro*. **J. Immunol.** 114:976-981 (1975).

3. **Rhodes, J.** Modulation of macrophage Fc receptor expression *in vitro* by insulin and cyclic nucleotides. **Nature** 257:597-599 (1975).

4. **Rhodes, J**. Altered expression of monocyte Fc receptors in malignant disease. **Nature** 265:253-255 (1977).

5. **Rhodes, J.** Regulatory effects of normal human monocytes and monocytes activated in cancer on normal lymphocyte responses to mitogen. In **"The Macrophage and Cancer".** K. James, W. McBride & A. Stuart eds. James McBride & Stuart, Edinburgh University (1977).

6. **Rhodes, J.**, Bishop, M. and Benfield, J. Tumour Surveillance: How tumours may resist macrophage mediated host defence. **Science** 203:199-182 (1979).

7. **Rhodes, J.** Resistance of tumour cells to macrophages. (Review) **Cancer Immunol. and Immunotherap.** 7:211-215 (1980).

8. **Rhodes, J.** and Oliver, S. Retinoids as regulators of macrophage function. **Immunology** 40:467-472 (1980)

9. **Rhodes, J.**, Plowman, P., Bishop, M. and Lipscomb, D. Human macrophage function in cancer: Systemic and local changes detected by an assay for Fc receptor expression. **J. Natl. Cancer Inst.** 66:423-429 (1981).

10. Persellin, R. and **Rhodes, J.** Inhibition of human monocyte Fc receptor and HLA-DR antigen expression by pregnancy alpha 2 glycoprotein (PAG). **Clin. Exp. Immunol.** 46:350-354 (1981).

11. **Rhodes, J.** and Stokes, P. Interferon-induced changes in the monocyte membrane: Inhibition by retinol and retinoic acid. **Immunology** 45:431-536 (1982).

12. Wildy, P., Gell, P.G.H., **Rhodes, J.** and Newton, A. The killing of Herpes Simplex virus by activated macrophages: a role for arginase. **Infection and Immunity** 37:4-45 (1982).

13. **Rhodes, J.** Human interferon action : reciprocal regulation by retinoic acid and β-carotene. **J. Natl. Cancer Inst.** 70:833-837 (1983).

14. **Rhodes, J.**, Jones, O.H., and Bleehen, N.M. Increased expression of human monocyte HLA-DR antigens and Fc receptors in response to human interferon *in vivo*. **Clin. Exp. Immunol.** 53:739-743 (1983).

15. **Rhodes, J.** Effects of tumours on the immune system. In '**Endocrine Aspects of Malignant Disease**' (R. Jung and K. Sikora eds.) pp.299-312. Heinemann Medical Books Ltd., London. (1984).

16. **Rhodes, J.**, Stokes, P. and Abrams, P. Human tumour-induced inhibition of monocyte function *in vitro*: reversal of inhibition by β-carotene (provitamin A). **Cancer Immunol. Immunother.** 16:189-192 (1984).

17. Eremin, O., Ashby, J. and **Rhodes, J.** Inhibition of antibody-dependent cellular cytotoxicity and natural cytotoxicity by retinoic acid. **Int. Arch. All. Appl. Immun.** 75:2-7 (1984).

18. Ward, K.N., Warrell, M.J., **Rhodes, J.**, Looareesuwan, S. and White, N.J. Altered expression of human monocyte Fc receptors in Plasmodium falciparum malaria. **Infect. Immun.** 44:623-626 (1984).

19. Wood, J.N., Coote, P.R. and **Rhodes, J.** Hydrocortisone inhibits prostaglandin production but not arachidonic acid release from cultured macrophages. **FEBS Letters** 174:143-146 (1984).

20. **Rhodes, J.**, Salmon, J. and Wood, J. Macrophage Fcγ2b receptor expression and receptor-mediated phospholipase activity : regulation by endogenous eicosanoids, **Euro. J. Immunol.** 15:222-227 (1985).

21. Wood, J.N., Coote, P.R., Salmon, J. and **Rhodes, J.** A small phospholipase inhibitory factor released by cultured cell-lines. **FEBS Letters** 189:202-206 (1985).

22. **Rhodes, J.**, Salmon, J. and Wood, J. Macrophage Fcγ2b receptor expression and receptor-mediated phospholipase activity : feedback regulation by metabolites of arachidonic acid. In: **'Prostaglandins Leukotrienes and Lipoxins'.** (Ed. J.M. Bailey.) pp.531-546, Plenum Press, New York (1985).

23. **Rhodes, J.**, Ivanyi, J. and Cozens, P. Antigen presentation by human monocytes : effect of modifying major histocompatibility complex class II antigen expression and interleukin 1 production by using recombinant interferons and corticosteroids. **Eur. J. Immunol.** 16:370-375 (1986).

24. **Rhodes, J.** Interleukin 1, interleukin 1 inhibitors and their role in inflammatory diseases. In: **'Lymphokines: The New Super-Drugs?'** Ed. P. Cozens. IBC Technical Services Ltd., London (1986).

25. **Rhodes, J.** Retinoids and Malignancy. **Lancet** 1987 Volume 2:1525 (1987).

26. **Rhodes, J.** and Tite, J. Functional Abolition of monocyte HLA-DR by aldehyde treatment: a novel approach to studies of class II restriction elements in antigen presentation. **J. Immunol.** 140:3344-3351 (1988).

27. Lui, D.S., Liew, F.Y and **Rhodes, J.** Immunoregulatory properties of novel specific inhibitors of 5-lipoxygenase. **Immunopharmacology** 17:1-9 (1989).

28. **Rhodes, J.** Evidence for an intercellular covalent reaction essential in antigen specific T cell activation. **J. Immunol.** 143:1482-1489 (1989).

29. Schmidt, J.A., **Rhodes, J.** and Bomford, R. Pharmacological manipulation of interleukin-1 synthesis, secretion or action. In, **'Interleukin-1, Inflammation and Disease'.** (R. Bomford and B. Henderson, eds) pp301-317 Elsevier Science Publishers Ltd, U.K. (1989).

30. **Rhodes, J.** Chemical events in immune induction: Evidence for a covalent intercellular reaction essential in antigen specific T cell activation: In, **'Immunological Adjuvants and Vaccines'.** (G. Gregoriadis, A. C. Allison and G. Poste, eds.) NATO/ASI Series A Vol. 179 Plenum Press, New York. pp.27-34 (1989).

31. Schmidt, J.A, Bomford, R., Gao, X-M. and **Rhodes, J.** 3 Deazaadenosine: An inhibitor of interleukin 1 production by human peripheral blood monocytes. **Int. J. Immunopharmacol.** 12:89-97 (1989).

32. Gao, X-M and **Rhodes, J.** An essential role for constitutive Schiff base-forming ligands in antigen presentation to murine T cell clones. **J. Immunol.** 144:2883-2890 (1990).

33. **Rhodes, J.** E-Rosettes provide an analogue for Schiff base formation in specific T cell activation. **J. Immunol.** 145: 463-469 (1990).

34. Brett, S.J. Blau, J., Hughes-Jenkins, C.M., **Rhodes, J.**, Liew, F.Y. and Tite, J.P. Human T cell recognition of influenza A nucleoprotein: Specificity and genetic restriction of immunodominant T helper cell epitopes. **J. Immunol.** 147: 948-991 (1991).

35. **Rhodes, J.**, Zheng, B. and Lifely M.R. Inhibition of specific T cell activation by monosaccharides is through their reactivity as aldehydes. **Immunology** 75: 629-631 (1992)

36. Zheng, B., Brett, S., Tite, J. P., Lifely, M. R., Brodie, T. A. and **Rhodes, J.** Galactose oxidation in the design of immunogenic vaccines. **Science** 256: 1560-1563 (1992).

37. **Rhodes, J.** Recent Advances in Vaccine Adjuvants. **Current Opinion in Therapeutic Patents** 2: 1833-1844 (1992).

38. Brett, S. J., **Rhodes, J.** Liew, F. Y. and Tite, J. P. Comparison of antigen presentation of influenza A nucleoprotein expressed in attenuated aroA Salmonella typhimurium with that of live virus. **J. Immunol.** 150: 2869-2884 (1993).

39. **Rhodes, J.**, Zheng, B. and Morrison, C. A. Galactose oxidation as a potent vaccine adjuvant strategy: Efficacy in murine models and in protection against a bovine parasitic infection. In *Combined vaccines and simultaneous administrations: Current issues and perspectives.* (eds. Williams, J. C., Goldenthal, K. L., Burns, D. & Lewis Jr., B. P.) **Annals New York Acad. Sci.** 754: 169-186 (1995)

40. **Rhodes, J.** The NAGO Adjuvant In '*Compendium of Vaccine Adjvuants and Excipients*' (eds. Powell, M. F. and Vogel, F. R.) Pharmaceutical Biotechnology Series, Plenum Publishing Corp., New York, NY 1995

41. Zheng, B., Brett, S. and **Rhodes J.** A role for carbonyl-amino condensation (Schiff base formation) in determining costimulation or specific unresponsiveness in human Th-cell clones. *Withdrawn from the publication process in 1991 for purposes of international patent filings by Wellcome plc*

42. **Rhodes, J.**, Zheng, B., Gao, X-M., Liew, F.Y. and Tite, J. Modulation of T cell responses by small Schiff base-forming molecules: further evidence for the Schiff base model of specific T cell activation. *Withdrawn from the publication process in 1991 for purposes of international patent filings by Wellcome plc*

43. **Rhodes, J.** , Chen, H., Hall, S.R. Beesley, J. E., Jenkins, D. C., Collins, P. and Zheng, B. Therapeutic potentiation of the immune system by costimulatory Schiff base-forming drugs. **Nature 377: 71-75 (1995)**

44. **Rhodes, J**. Therapeutic potential of Schiff base forming drugs. **Expert Opin. Invest. Drugs 5**:257-268 (1996)

45. **Rhodes, J**. Covalent chemical events in immune induction: Fundamental and therapeutic aspects. **Immunology Today 17**:436-441 (1996)

46. Chen, H. and **Rhodes, J**. Schiff base forming drugs: mechanisms of immune potentiation and therapeutic potetial. **Journal of Molecular Medicine 74**:497-504 (1996)

47. **Rhodes, J**. Chen, H., Hall, S. R., Beesley, J. E. Jenkins, D. C., Collins, P. and Zheng, B. Prophylactic and Therapeutic Potentiation of the Immune System by Costimulatory Schiff base-forming drugs. In ***Vaccines: New Advances in Technologies and Applications***. IBC Biomedical Library Series (Eds. Ostriker, R. and Savage, L.M.) Section 7.3: 1-22 (1996)

48. Chen, H. Hall, S. Zheng, B. and **Rhodes, J.** Potentiation of the immune system by Schiff base-forming drugs: Mechanism of action and therapeutic potential. **BioDrugs**. 7:217-231 (1997)

49. Chen, H., Hall, S. R., Beesley, J. E. **Rhodes, J.**, Zheng, B. and Jenkins, D. C. The Immunpotentiatory Drug Tucaresol: Mechanism of Action and Therapeutic Applications. in **Vaccines II: New Advances in Technologies and Applications**. IBC Library Series (Eds. Thibeault, C. A. and Savage, L. M.) pp79-111 (1997)

50. Chen, H., Hall, S., Heffernan, B. Thompson, N. T., Rogers, M. V. and **Rhodes, J.** Convergence of Schiff base costimulatory signaling and T-cell receptor signaling at the level of mitogen activated protein kinase ERK2. **J. Immunol. 159**: 2274-2281 (1997).

51. Rhodes, J. Intercellular covalent chemical events in T-cell activation as targets for the development of immunopotentiatory drugs. **Current Trends in Immunology 1**:17-28 (1998).

52. Smith, A. C., Yardly, V., **Rhodes, J.** and Croft, S.L. Activity of the novel immunomodulatoary compound tucaresol against experimental visceral leishmaniasis **Antimicrobial Agents and Chemotherapy, 44:** 1494-1498 (2000)

53. Clerici, M., Bosis, S., Rizzardini, G. Colombo, F., **Rhodes, J.**, Bray, D. Piconi, S. In vitro immunomodulatory properties of tucaresol in HIV infection. **Clinical Immunol. 97**: 211-220 (2000)

54. Hall, S. R. and **Rhodes, J.** Schiff base mediated costimulation primes the TCR-dependent calcium signalling pathway in CD4 T-cells. **Immunology 104**:50-57 (2001).

55. Rhodes, J. Discovery of immunopotentiatory drugs: Current and future strategies. **Clin. Exp. Immunol. 130**:363-367 (2002)

PATENTS

1. **INTERNATIONAL PATENT P.C.T. patent application NAGO adjuvant (Europe - all countries, Japan, U.S.A.) Compositions for vaccines filed 16th August 1991. (Wellcome Foundation Ltd. U.K. Rhodes, J. - inventor).**

2. **GPA Family PA1408: Use of 589C80 (tucaresol) and analogues as immunostimulants.** Formal title **Immunopotentiatory Agents and Physiologically Acceptable Salts Thereof. Filing data 1st October 1993 Rhodes, J. - inventor.**

3. **GPAD PA1391 USA (26th Aug '93), Japan 30 Sept. '93 and Europe (17th Sept. '93) Use of 589C80 as an immunopotentiator. Rhodes, J. - inventor.**

4. **GPA Family PA 1586 - Use of Proguanil as an Immunopotentiator. Priority filing date 20th December 1994 Rhodes, J. & Hudson A. inventors**

5. **Case No. PG4160 CMV Exon 1 as transcriptional regulatory sequence Ellis J, Ertl, P. & Rhodes, J. Inventors**

ACADEMIC AND EXTRAMURAL RESPONSIBILITIES

Fellow of the Royal College of Pathologists

Editorial Board Member, *Clinical and Experimental Immunology 1994-2002*

Peer Reviewer for Medical Research Council and Arthritis and Rheumatism Council grant applications.

Supervision of PhD students jointly with academic supervisors in the University of London

Examination of PhD students in the University of London

Serving Member, UK International Technology Mission on Vaccines, Department of Trade and Industry mission to the USA, March 2000